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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,111	03/10/2004	Dario Norberto R. Carrara	88066-7900	5916

28765 7590 03/04/2009

WINSTON & STRAWN LLP
PATENT DEPARTMENT
1700 K STREET, N.W.
WASHINGTON, DC 20006

EXAMINER	
SCHLIENTZ, NATHAN W	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
03/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,111	CARRARA ET AL.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,13,15-31,37,38,40-47 and 56-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,13,15-31,37,38,40-47 and 56-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner for your application in the USPTO has changed. Examiner Nathan Schlientz can be reached at 571-272-9924.

Status of Claims

Claims 1, 3-11, 13, 15-31, 37, 38, 40-47 and 56-67 are pending and will presently be examined on the merits for patentability. No claim is allowed at this time.

Allowable Subject Matter

The indicated allowability of claims 37-47, 59 and 61-63 is withdrawn in view of the newly discovered references discussed herein below. Rejections based on the newly cited references follow.

Claim Objections

1. Claim 11 is objected to because of the following informalities: the claim recites further comprising a buffering agent as well as a buffer. The claim also places a semicolon between neutralizing agent and buffering agent, but places commas between the other components listed. Appropriate correction is required.

2. Claim 27 is objected to because of the following informalities: the 4th line of the claim states "estriol, succinate", but it is believed Applicants intended to state "estriol succinate". Appropriate correction is required.

3. Claim 30 is objected to because of the following informalities: the claim states methandrostenolate, but the instant specification does not provide support for this compound, and the examiner is unable to determine the structure of this compound. The instant specification does however provide support for methandrostenolone. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1, 5-7, 11 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Carrara et al. (WO 02/11768 A1).

Carrara et al. disclose a composition comprising 1.25 wt.% testosterone, 5.00 wt.% diethylene glycol monoethyl ether (Transcutol P), 5.95 wt.% propylene glycol, 43.09 wt.% ethyl alcohol, 43.07 wt.% water, 1.20 wt.% carbomer (Carbopol 980 NF, a gelling agent), 0.38 wt.% triethanolamine (a neutralizing agent), and 0.059 wt.% disodium EDTA (a sequestering agent) (Example 2).

As noted by Applicants on page 11 of their response filed 10 November 2008, Example 2 of Carrara et al. does not contain a long chain fatty alcohol or long chain fatty acid.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1, 5, 6, 8-11, 13, 15-28, 37, 38, 40-47, 56-58 and 61-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mak et al. (US 6,319,913) in view of Bechgaard et al. (US 5,397,771).

Applicant's claims

Applicants claim a gel formulation comprising a sex hormone, a gelling agent, an alkanol, a polyalcohol (propylene glycol), and a permeation enhancer (i.e., tetraglycol furol), wherein the formulation is substantially free of long-chain fatty alcohols, long-

chain fatty acids, and long-chain fatty esters; as well as a kit containing said composition and a method for treating hormonal disorders by administering said composition.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Mak et al. teach gel formulations comprising an active ingredient, a penetration enhancing system, a glycol and a gelling agent (col. 2, ln. 19-32). Mak et al. teach that the active ingredient includes hormones, such as testosterone, estradiol and a testosterone derivative, at a concentration of about 0.1 to about 10 wt.%, preferably about 0.1 to 5 wt.%, more preferably about 1 to about 2 wt.% (col. 4, ln. 1-8) and antioxidants; the penetration enhancing system includes oleic acid at about 0.1 to about 5 wt.%, a C_1-C_4 alcohol (i.e., ethanol, propanol and isopropanol) at about 5 to about 55 wt.%, preferably about 10 to about 40 wt.%, more preferably about 25 to about 35 wt.%, and a glycol (i.e., propylene glycol) at about 25 to about 55 wt.%, preferably about 30 to about 40 wt.% (col. 3, ln. 14-16; col. 4, ln. 9-59); and the gelling agent (i.e., carbomer) at about 1 to about 10 wt.%, preferably about 1 to about 5 wt.%, more preferably about 1 to about 3 wt.% (col. 3, ln. 60 - col. 4, ln. 18). See Tables 1-4 and Examples 1-9 for specific formulations.

Mak et al. teach that the addition of oleic acid resulted in reduced irritation compared to the addition of oleyl alcohol (Example 1), especially in combination with a gelling agent, such as carbomer (col. 4, ln. 20-24). Mak et al. further teach additional irritation reducers added to the formulations (Examples 2-9), and state that while the

combination of oleic acid and gelling agent (Carbopol) produced very low irritating formulations, the incorporation of other irritation reducing agents can further decrease irritation (col. 10, ln. 46-49). Mak et al. also teach that the compositions are suitable for the treatment of menopausal symptoms (col. 5, ln. 55-56) and have utility in people and other mammals suffering with systemic testosterone deficient disorders, wherein these formulations can be used to deliver testosterone locally, and thus can be used in conditions where increase in local testosterone concentration is beneficial (col. 10, ln. 27-34).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Mak et al. do not teach gel formulations comprising a permeation enhancer and not comprising oleic acid, as instantly claimed. However, Bechgaard et al. teach 0.1 to 30 wt.%, preferably 0.1 to 20 wt.%, more preferably 1 to 15 wt.% of a n-glycofurol in combination with propylene glycol as a permeation enhancer suitable for intranasal administration of adrenal hormones and sex hormones, such as ethinyloestradiol, levonorgestrel, FSH, LH, LTH, estradiol-17-beta, progesterone, norethindrone, testosterone, etc. and derivatives or analogues thereof (col. 5, ln. 37-40; col. 7, ln. 34-42; and col. 8, ln. 5-26 and 67-68). Bechgaard et al. teach that their formulations are suitable for systemic administration through the mucosa of the nose, mouth or vagina (col. 9, ln. 1-5). Furthermore, Bechgaard et al. teach that n-glycofurols are considered to be a pharmaceutically acceptable carrier, especially a pharmaceutically acceptable carrier for nasal administration, wherein n-glycofurols are considered as an enhancer

facilitating the uptake of biologically active substance through a mucosal membrane of a mammal, especially through the mucosa of the nose (col. 9, ln. 6-13). Bechgaard et al. further teach that intranasal administration of n-glycofurol may act just as quickly as intravenous injection (col. 26, ln. 48-50). Bechgaard et al. teach that additional pharmaceutical excipients may be included such as surfactants and pH-controlling agents (i.e., buffers) (col. 10, ln. 50-52 and 67-68). Also, Bechgaard et al. teach dispensing their compositions from a Pfeiffer pump unit delivering 50 when activated (col. 14, ln. 30-32).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to substitute n-glycofurol in the place of oleic acid in the formulations of Mak et al. because Bechgaard et al. teach that n-glycofurol is a suitable permeation enhancer for mucosal administration of sex hormones, wherein n-glycofurol may act just as quickly as intravenous administration.

Also, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute n-glycofurol as a functional equivalent to oleic acid as taught by Mak et al. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable

results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143.

In the instant case, the substituted components (oleic acid and n-glycofurol) and their functions were known in the art at the time of the instant invention. For example, Mak et al. teaches oleic acid as a permeation enhancer for administration of sex hormones via the mucosa. Bechgaard et al. teaches n-glycofurol as a permeation enhancer for administration of sex hormones via the mucosa. One of ordinary skill in the art could have substituted one known permeation enhancer for another, and the results of the substitution would have been predictable, that is enhanced permeation of the sex hormone through the mucosa.

With regard to the dosage amount and serum levels of hormone, the amounts of hormone in the system that are effective to treat various conditions is well-known to one of ordinary skill in the art. Therefore, it would be within the level of ordinary skill to determine the amount of hormone necessary to achieve therapeutic serum levels. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc.,

874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

2. Claims 1, 3-11, 13, 15-31, 37, 38, 40-47 and 56-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mak et al. (US 6,319,913) in view of Bechgaard et al. (US 5,397,771), further in view of Dudley et al. (US 6,503,894) and Labrie (US 5,955,455).

Applicant's claims

Applicants claim a gel formulation comprising a sex hormone, a gelling agent, an alkanol, a polyalcohol (propylene glycol), and a permeation enhancer (i.e., tetraglycol furol), wherein the formulation is substantially free of long-chain fatty alcohols, long-chain fatty acids, and long-chain fatty esters; as well as a kit containing said composition and a method for treating hormonal disorders by administering said composition.

Determination of the scope and content of the prior art

(MPEP 2141.01)

The teachings of Mak et al. and Bechgaard et al. are discussed above and incorporated herein by reference.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Mak et al. and Bechgaard et al. do not teach treating hypogonadism, or the administration of methyltestosterone with methandrostenolone. However, Dudley et al. teach a gel formulation for the treatment of hypogonadism comprising an androgen, alcohol, and penetration enhancer (Abstract), wherein the androgens include testosterone, methyltestosterone, and methandrostenolone (col. 11, ln. 65-66; col. 12, ln. 1 and 17-22; and Table 5). Dudley et al. further teach that suitable penetration enhancers include diethylene glycol monoethyl ether (col. 12, ln. 54-55).

Also, Labrie teaches that dehydroepiandrosterone (DHEA) is useful for the treatment of hypogonadism and conditions related to decreased secretion of sex steroid precursors by the adrenals (Abstract).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to treat hypogonadism with the compositions of Mak et al., using as the androgen testosterone, methyltestosterone, methandrostenolone, DHEA or combinations thereof, and as the penetration enhancer either n-glycofurol or diethylene glycol monoethyl ether, as reasonably taught by Bechgaard et al. and Dudley et al.

With regard to the combination of methyltestosterone and methandrostenolone, such would have been obvious in the absence of evidence to the contrary because it is generally prima facie obvious to use in combination two or more ingredients that have previously been used separately for the same purpose to form a third composition useful for that same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. *In re Kerkhoven* 626 F.2d 646, 850, 205 USPQ 1069, 1072 (CCPA 1980).

With regard to the dosage amount and serum levels of hormone, the amounts of hormone in the system that are effective to treat various conditions is well-known to one of ordinary skill in the art. Therefore, it would be within the level of ordinary skill to determine the amount of hormone necessary to achieve therapeutic serum levels. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is 571-272-9924. The examiner can normally be reached on 8:30 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/
Primary Examiner, Art Unit 1616